NOVEMBER 2019

Incentivising a sustainable response to the threat of AMR

About the BEAM Alliance

The BEAM Alliance (**B**iotech companies from **E**urope innovating in **A**nti-**M**icrobial resistance research) represents over 60 European SMEs that develop solutions to fight antimicrobial resistance at a European and national level. The BEAM members are collectively developing over 140 new, diversified R&D projects focused upon prevention, diagnosis and cure of microbial infections. The goal of the BEAM Alliance is to maintain and promote awareness of SME-driven innovation in the field and to support policymakers in understanding economic business models around AMR. The BEAM Alliance closely cooperates with all stakeholders dedicated to the fight against AMR. Although being a member of and closely collaborating with the AMR Industry Alliance to curb antimicrobial resistance, the BEAM Alliance is advocating for the specific SME needs with regards to investment in R&D to meet public health needs with new innovative diagnostics and treatments.

Key messages

- **Antimicrobial resistance (AMR) is facing a market failure that has already jeopardised the development of valuable AMR products**
- **Evaluation should capture the societal benefit of AMR products, while reimbursement framework should guarantee best medical care, informed by precise diagnosis and delivery of optimal preventative or curative therapy**
- **Partially delinked market uptake support is required to de-risk the capital-intensive product launch, but interim incentives must also be designed to recoup investment made by the whole discovery and development value chain**
- **As the cornerstone of the global medical infrastructure, antimicrobials should benefit from the support of other benefiting therapeutic areas**
- **To allow for a sustainable management of the AMR crisis, incentives should assign priority to truly innovative and differentiated products**
- **In the absence of immediate action, the whole AMR-focused SME landscape and key skill sets may be lost.**

When market failure can lead to societal disaster

That humans live longer and healthier lives today compared to our forefathers is to a large extent dependent on advances in medicine, in particular pharmaceutical products that treat illness. This is especially so for antibiotics which have provided the means to treat and cure otherwise life-threatening infections. Recall an estimated 30% of the European population died from the 'black-death' (caused by *Yersinia pestis*) in the 17th century, today completely curable with a course of antibiotics. Antibiotics are the single biggest pharmaceutical drug class used across global healthcare systems. Data from the New England Journal of Medicine show that in the US approximately half of all individuals received an antibiotic prescription within a 2 years period[1].

Over time the pharmaceutical industry kept pace with the emergence and spread of bacterial antibiotic resistance through the discovery and development of new antibiotics. Antibiotics, which can cure a patient who would otherwise die from infection are unfortunately taken for granted and as a result, have become significantly undervalued. The expectation of antibiotics as low-cost pharmaceutical products, in a market dominated by generics, combined with the slow uptake of newly approved compounds, has led to a complete erosion of the therapeutic area.

Most of the big pharma players no longer invest in this therapeutic area and therefore these companies no longer represent the source of much needed new agents. Most of the pharmaceutical companies still working in the area are so-called Small and Medium Enterprise (SMEs) who are arguably the sole source of innovation that is driving the discovery and early clinical phase development of new antibiotics. These companies now find themselves operating at a time where investor sentiment has completely deteriorated and the ability to secure investment has become an acute concern.

Unless this situation changes dramatically, most SMEs will struggle to survive beyond the near future (<2 years), as investment in the therapeutic area is in danger of grinding to a halt. The challenge is highlighted by the demise of 'successful' SMEs such as *Achaogen* despite bringing important new antibiotics to market. An increasing number of product developers, even when strongly sponsored by public funds, are struggling to find the complementary private co-funding.

The emergence of resistance continues unabated and we are rapidly approaching a situation where an alarming number of resistant infections are not successfully treated due to a lack of an effective antibiotic.

To address the issue, a set of financial and regulatory incentives are being contemplated, all with pros and cons. No single mechanism will solve the problem alone. Although we acknowledge the complexity of the task, we call for immediate actions; otherwise, the favoured solutions will arrive too late to save the infrastructure and expertise to deliver much needed new anti-infectives.

Key Actionable Areas:

- **Align antimicrobial value and pricing with the true societal benefit**
- **Enable appropriate reimbursement paired with appropriate antimicrobial use**
- **Guarantee a minimal market footprint at product launch**
- **Foster financial contributions from medical areas benefiting from antimicrobial use**
- **Guarantee an acceptable investment profile supporting early R&D**
- **Encourage innovative and diversified interventions against AMR**

[1] Olesen S.W. et al. *N Engl J Med* **380**:1872 (2019)

Action needed to align antimicrobial value and pricing with the true societal benefit

The tremendous societal value demonstrated by antimicrobials is not currently reflected in the valuation and pricing mechanisms for these drugs.

New drug candidates are commonly tested against generic products (as standard-of-care market comparators) in non-inferiority trials. As a consequence, Health Technology Assessment (HTA) agencies may adopt an unfavourable valuation for the new candidate by benchmarking it against the cost of the generic agent, based on their assessment only on currently established criteria (Figure 1). However, effective antimicrobials are drugs that can completely cure patients that may otherwise die within a few days.

Importantly, antimicrobials not only provide substantial value through those established HTA assessment criteria, but they also address more global public health issues that go beyond a narrow patient-centric approach[2] (Figure 1). These non-typical criteria would enable us to value true additional benefits and consider antimicrobials and any innovative AMR product[3] as public goods that are integral to sustaining healthcare systems. Indeed, as mentioned recently, "*the role antibiotics now play in disease prevention for surgery and chemotherapy […] suggests that antibiotics have become part of the health infrastructure such that they shape possibilities and constraints in pathways to health*."[4]

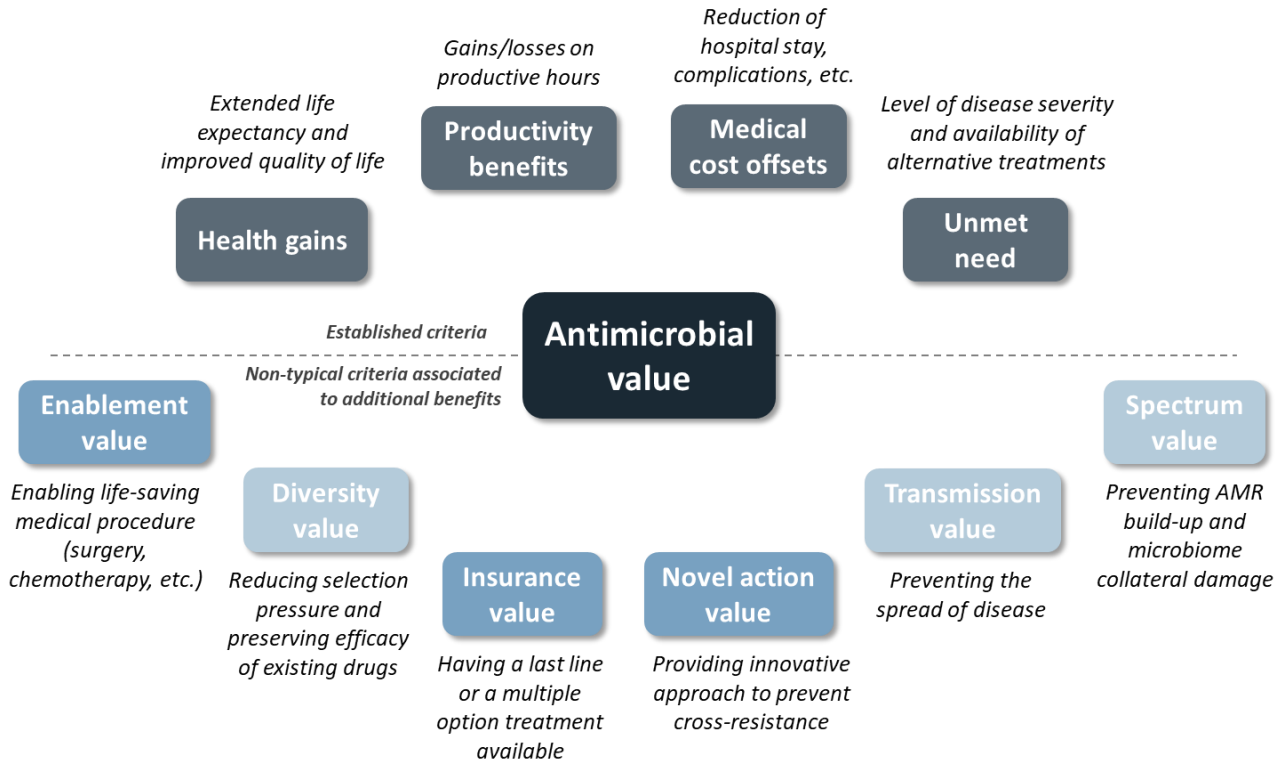

Figure 1: Established and non-typical potential additional benefits to consider in HTA valuation of AMR Products (adapted from 2)

These considerations would allow a better evaluation of the contribution AMR products bring to society and should be recognised by HTA agencies; there is an urgent need for HTAs to modernize their approach to reflect this. A more comprehensive framework needs to be setup at the European level, probably with the

[2] https://www.ohe.org/publications/additional-elements-value-health-technology-assessment-decisions
[3] AMR Products are healthcare products which address the AMR Medical need, including drugs, medical devices, in vitro diagnostics, as novel solutions for prevention, diagnosis and cure of microbial infections (see 9)
[4] Chandler C.I.R *Palgrave Communications* **5**: 53 (2019)

support of the EUnetHTA network, whose aim is to facilitate scientific and technical cooperation between the European HTA bodies.

Action needed to ensure fair reimbursement of the most suitable antimicrobial solutions

Reimbursement is the original and most known PULL incentive, as it gives the security that if the R&D has been properly done and addresses unmet medical need, there is a price for it. The current EU/US reimbursement systems (e.g., DRG) provide lump sum payments, scaled on the price of currently used drugs, for a given patient medical status. To prevent overspending beyond the reimbursement threshold, physicians often avoid diagnosis testing and prescribe cheap, broad-spectrum generic antibiotics. This leads to a cost-driven approach of patient management over medical benefit and wider One Health concerns.

However, these apparent savings are deleterious in the fight against AMR and are, at least partly, responsible for the ongoing crisis.

Improved and differentiated therapeutic options (e.g. narrow spectrum) may be available and their use can be informed with the support of relevant diagnostic testing. This empowers good stewardship to ensure the most suitable treatment is deployed, whereas today, the differentiation criteria are essentially limited to toxicity profiles and spectrum/dose of efficacy.

Although the strategy might look more expensive at first sight, it will drive lower morbidity and mortality, reduced length of hospital stays, reduced spread of resistance and increased antimicrobial conservation.

Therefore, **reimbursement outside, or complementary to, the DRG system should be sought for antimicrobial strategies offering tailored patient management**.

Such a system is now being considered in US through the DISARM 2019 bill which is actively supported by the BEAM Alliance. Similar incentives must be considered in Europe and ideally, to decrease the financial and administrative burden of launching a product here, the introduction of a common template of reimbursement practices should be implemented across EU member countries.

Action needed to guarantee a minimal market footprint at product launch

A striking feature of recent antimicrobial market launches is the very slow market uptake. Drugs 2 years post-commercialization (such as Vabomere® – *Melinta Therapeutics*) struggle to reach $11 million annual turnover. The sales of Zemdri® (*Achaogen*'s product approved by FDA on June 2018) for the first six months were only $783,000 whilst reported yearly net loss peaked at $186 million. Failure in the face of success. Meagre sales are the mechanical counterpart of stewardship principles that encourage the limited use of new drugs to preserve effectiveness.

This is particularly impactful for AMR-focused SMEs with expertise in R&D but forced to launch their product themselves. Substantial further investment is needed for this expensive commercialization step which then collides with the broken market system that antibiotics currently operate in. This second valley of death is frequently characterized by anaemic market uptake at launch and drastic cut of R&D staff (crucial loss of AMR know-how and skills). This landscape can be perceived as irrecoverable by investors, resulting in a further loss of investor appetite for the area. The challenge was magnified recently by the demise of

Achaogen, which occurred despite a significant portion of development costs being offset by non-dilutive funding from BARDA.

Thus, **a type of buying commitment or market uptake support provided by a national central pharmacy for a newly released drug would bring tangible financial benefits to the developer**. It would both guarantee a minimal annual return to the drug developer for the few first year(s) after launch while helping the global community to organize the sustainable use of a new antimicrobial. Contractual frameworks may be setup country-by-country with figures based on the population size. Indeed, the UK government has recently (July 2019) confirmed its intent to pilot a 'subscription' style model that pays pharmaceutical companies upfront for access to drugs based on their usefulness to the NHS. The program will be evaluated from the start and findings will be shared with the rest of the world so that other healthcare systems can test similar models.
Other options to guarantee a minimal revenue at launch include the Market Entry Reward (MER), that can further be derived into the Priority Antimicrobial Value and Entry (PAVE) Award developed by Duke Margolis[5] combining MER and subscription model over time.

A fully delinked model completely shifts financial uncertainty to the payer and put an excessive risk on the payer's shoulders when predicting resistance patterns and future innovation needs[6]. **SMEs are advocating for a partial de-linkage where an annual fee is paid by the healthcare system to get access to an agreed amount of the drug (which helps in assuring cost-effective drug manufacture and supply) and each thereafter dose is paid on a per-use basis.**

Action needed to foster financial contributions from medical areas benefiting from antimicrobial use

Healthcare systems are paying heavy costs in many therapeutic settings to prolong life (e.g., cancer) but seem reluctant to pay for treatment of a potentially deadly infection that impacts that process. Antimicrobials have already demonstrated pivotal utility across the length and breadth of medical care globally. As such the spectre of antimicrobial resistance and the need to ensure a rich and effective pipeline of antimicrobials potentially impacts all therapeutic areas.

A "Play or Pay" policy[7], where companies not investing into AMR R&D are subject to a surcharge, may be a useful mechanism to generate funds to support antimicrobial development and reimbursement. However, the details of such a system and criteria for inclusion or exclusion are yet poorly defined. Also, it is highly probable that the knock-on effect would be that such surcharges would pass right back to consumers/health systems through higher pricing policies from the penalised companies.

The Transferable Exclusivity Extension (TEE) voucher might be a better controlled mechanism to pass along the costs across therapeutic areas. It also levers immediate financial incentives without the challenge of requiring immediate and significant funds. The voucher is awarded to a newly approved designated antimicrobial product and provides a prolonged exclusivity period that can be applied to an already commercialized drug in any therapeutic area. TEE could in principle be used by the awarded company for a product of its own portfolio or sold to a third party to be assigned to one of their assets.

[5] https://healthpolicy.duke.edu/sites/default/files/atoms/files/value-based_strategies_for_encouraging_new_development_of_antimicrobial_drugs.pdf
[6] Bhatti T. et al. J. The Journal of Law, Medicine & Ethics, 46 S1 (2018):59-65
[7] https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

As a TEE would prolong the revenue stream for high selling drugs, key guardrails must be attached to ensure patient access and protect national health systems from over-expenditure, for example through a maximum revenue cap. The generic industry should also benefit from some guarantees, e.g., through a minimal remaining exclusivity period of the recipient drug. TEE combines the support from other medical areas with the financial incentive to deliver a new AMR product to the market. To date attempts to progress the TEE concept have met resistance from civil society groups that cite concerns over delays for affordable access to lifechanging medication. Additionally, there is political and public concern over the perceived handouts that large pharma could benefit from as a result of acquiring the TEE for an existing blockbuster product.

Action needed to guarantee an acceptable investment profile supporting early R&D

In a traditional biotech business model, an SME would raise money from private investors and develop its product up to clinical phase I or II, and then sign a licence agreement with a big corporation, in charge of finalizing the clinical development and organizing the commercialization. The licence comes with premarketing revenues (upfront and milestones) that offers a preliminary reward of the risk taken by the SME and its private investors. But as bargain power rules everything, the least potential licensees you have, the worst the licensing financial conditions you get. Nowadays, there are very few pharma players in the field, with no/very limited willingness for in-licensing; therefore, the deals signed for the past decade didn't pay off the investment made by the private investor in the biotech.

But what is the real financial power of a PULL mechanism, as featured in currently on-going discussions, to fix the problem? Would a late-stage revenue stream, like *e.g.*, the Market Entry Reward (MER), allow to revive the biotech business model and correctly award private investors back?

Imagine a SME at preclinical stage going for Series A funding, ten years ahead of commercialization, where a billion 1 USD prize, equally spread over a 4-year period, is expected. Risk adjust (Table 1) by the Probability of Success (PoS) that the drug is approved from Series A funding to market (anything between 5 and 10% from early stage perspective, so let's take 7%). The discount rate for early stage SMEs is in the range of 18%. This brings you to a risk-adjusted net present value (rNPV) of million 10.6 USD, if and only if the SME gets 100% of the MER, which is unrealistic unless the SME goes up to market launch. And if so, the level of negative cash flow to consider would be by far above.

	Series A	R&D	Commercialization			
	2020	…	2030	2031	2032	2033
MER (USDm)			250	250	250	250
PoS			7%	7%	7%	7%
Discount			19%	16%	14%	12%
rnCF (USDm)			3.3	2.8	2.4	2.0
rNPV (USDm)	**10.6**					

Table 1: rNPV calculation for a product benefiting from a billion 1$ market entry award after 10 years.
PoS: probability of success; rnCF: risk-adjusted net cash flow; rNPV: risk-adjusted net present value.

This demonstration simply points out that PULL incentives, as currently thought, mostly intends to reward the commercialization phase, but are unable to adequately reward the whole R&D value chain (biotechs and potentially their academic licensors) and attract investors for early-stage developments.

Guardrails are thus mandatory to enforce appropriate financial feedback for R&D developers. Distribution of the prize amount over the different phases of development is an option, that would reproduce the upfront/milestone incomes of the traditional biotech model. A recent report commissioned by the Public Health Agency of Sweden[8] highlighted the benefit of milestone prizes delivered upon successful completion of IND filing, phase 1 and, to a lesser extent, phase 2. The proposed modelling underlined the incentive cost-effectiveness per launched antibiotic.

However, the milestone prize concept does not offset the need for a substantial and sustainable source of money, as for MER, and it needs a set of guardrails to ensure the awarded products are further developed up to market uptake (although methods to retain trader loyalty from the banking industry could apply). As SMEs are probably the most concerned by milestone prizes, the BEAM Alliance is welcoming any stakeholder invitation to further discuss the issue.

Actions needed to encourage innovative and diversified interventions against AMR

The 2017 analysis by WHO of antibacterial agents in clinical development highlighted the very limited level of innovation. Novelty from an intellectual property (IP) perspective does not guarantee innovation. IP-valid new drugs can simply be derived from old drugs, offering easier, well-known (and probably faster) paths to the market. Still, they may not enlarge the medical armamentarium in a sustainable manner, as resistant strains may arise quickly after launch.

We need new antimicrobials with new mechanisms of action, but innovation can also come from repurposed old drugs or combination. These models are often not popular with market, although they could truly contribute to curb specific AMR threats in an economical manner if evaluated properly. In that regard, it is important that consideration is given to ensure the set of incentives discussed above can be awarded based on defined performance criteria considering all benefits of those products (see Figure 1), and not on a "first come, first served" basis.

We believe overall that there is a need for diversified types of interventions to combat the AMR public health need. Indeed, a diversified pipeline of solutions has the best chance to prevent and/or to cope with the breadth of resistance that might emerge (see *The BEAM Alliance new vision of AMR innovation memo*[9]). Which leads to the challenge of properly evaluating the performance of such an extended set of antimicrobial actions (see Figure 1) to ensure the access to market to a rich and sustainable pipeline of new products.

[8] http://uu.diva-portal.org/smash/get/diva2:1283298/FULLTEXT01.pdf
[9] https://beam-alliance.eu/wp-content/uploads/2019/04/beam-alliance-a-new-vision-to-support-amr-innovation.pdf

Conclusion

Each measure outlined above (and summarized in Figure 2) can bring part of the solution. They must however be **accompanied by key guardrails to protect the healthcare systems and make sure the incentive adequately rewards quality products and their developers**.

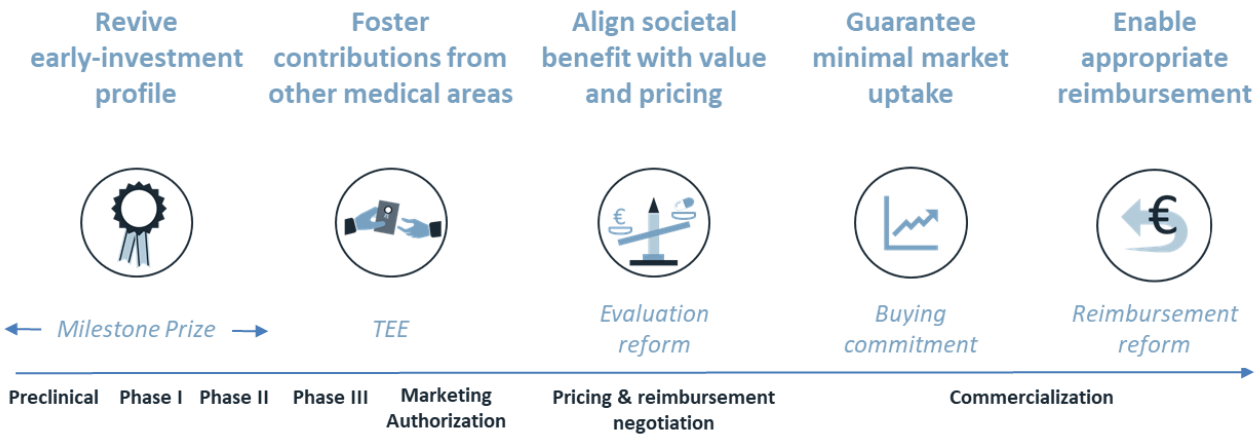

Figure 2: A set of incentives to revive the AMR field

Crucially, time is against us. Investors continue to leave the field, jeopardizing the short-term future of biotech companies. **Without adequate incentives it is anticipated that in less than 2 years from now, many AMR SMEs will have disappeared together with their innovative products and expert teams**.

We are grateful to national governments (e.g., US, UK, Sweden) announcing pilot actions and full regulations. We also applaud initiatives by GARDP and other AMR-specific approaches in preparation/consultation (e.g. WHO/EIB AMR Fund). However, the required support to revive the AMR field, curb the related threat and deliver a sustainable solution is on a far larger scale. **We urgently request that other public authorities quickly follow the lead and deliver the required policy changes in this crucial area**.

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